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Who plays the strings in newborn analgesia at birth, vasopressin or oxytocin?

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For many years, oxytocin has been viewed as the primary hormone edging endocrinology, behavior, and pain in mothers and infants around parturition. Very recent work puts the vasopressin receptor 1A in the focus of peripheral analgesia and pain relief in respect to circulating vasopressin and oxytocin. Here, we present a concise overview on these new findings, will discuss them in context of parturition, and will outline new avenues.

Both neuropeptides, oxytocin and vasopressin, are synthesized in the hypothalamus from paraventricular and supraoptic nuclei and act either centrally within the brain or peripherally after release by the posterior pituitary gland (Meyer-Lindenberg et al., 2011). In mammals, four receptors have been identified, the oxytocin receptor (OTR) and three receptors that respond primarily to vasopressin, vasopressin receptor 1A (VR1A), VR1B, and VR2. Whereas VR1A and VR2 mediate the vasoactive and antidiuretic action, respectively, in the periphery, central vasopressin functions are mediated by VR1A, VR1B, and OTR. Ligand binding of both centrally acting receptors, OTR and VR1A, activates the phospholipase C beta signal transduction pathway (Jard et al., 1986; Arnaudeau et al., 1994; Ku et al., 1995; Phaneuf et al., 1995). Both the soluble ligands, oxytocin and vasopressin, as well as their receptors, OTR and VR1A, display high sequence homology, hence both ligands can activate both receptors (Chini and Manning, 2007).

In contrast to humans, the development of paraventricular and supraoptic nuclei is late in rodents (Clancy et al., 2001). Synthesis of vasopressin in rats starts between the 16th and 18th day of intrauterine life and that of oxytocin few days after birth (Lipari et al., 2001). As the placenta of rodents is freely passable for both neuropeptides, the newborn rodent oxytocin is mainly provided by the mother. On the

contrary, fetal human oxytocin at birth is of fetal origin, because its concentrations are higher in the umbilical artery than in the umbilical vein, and oxytocin is completely absent in cord blood of anencephalic newborns (Chard et al., 1971).

Parturition is a very complex process and oxytocin has its role particularly in contractility of myocytes (Smith, 2007). Exogenous oxytocin administration to pregnant woman strongly induces contractions (Mori et al., 2011) but plasma oxytocin does not cross placenta toward the fetus (Chard et al., 1971; Patient et al., 1999). However, by use of an *in vitro* system with dually perfused isolated cotyledons from term human placenta, bi-directional diffusion of oxytocin has been demonstrated across the maternal-fetal barrier (Malek et al., 1996). Fetal oxytocin concentrations have been found to be either unaffected by vaginal delivery, contractions, and by experimental hypoxic stress (Stegner et al., 1984; Thornton et al., 1993; Patient et al., 1999) or slightly increased (1.5- to 2-fold) in umbilical cord blood after vaginal delivery as compared to elective cesarean section (Marchini et al., 1988; Lindow et al., 1998). Hence, fetal oxytocin release is not subject to birth stress and even if there is some crossing of the maternal-fetal barrier, fetal oxytocin levels are barely altered. This is in sharp contrast to what has been observed for vasopressin. During vaginal delivery, there is an extremely steep rise of circulating vasopressin which is unparalleled by any changes that may occur during the life span of a human being (Chard et al., 1971; Polin et al., 1977; Wellmann et al., 2010; Benzing et al., 2011; Schlapbach et al., 2011). The exceptional surge of circulating vasopressin (approximately 100-fold) is observed in infants born by vaginal delivery but not those born by elective cesarean section.

A perpetually growing body of literature within the last four decades demonstrate analgesic effects in human and rodents of both, oxytocin and vasopressin (Honda and Takano, 2009; Koshimizu and Tsujimoto, 2009; Schorscher-Petcu et al., 2010). Oxytocin was reported to be analgesic when administered into the brain (Ge et al., 2002; Gao and Yu, 2004), the spinal cord (Yu et al., 2003; Miranda-Cardenas et al., 2006; Condes-Lara et al., 2007), or systemically (Lundeberg et al., 1994; Reeta et al., 2006). Very recently, oxytocin was investigated in newborn Wistar rats in the tail-flick pain assay and the vocalization assay of decerebrated newborn pups (Mazzuca et al., 2011). Whereas systemically (intraperitoneally) administered oxytocin was found to augment newborn rat analgesia, while two OTR antagonists, atosiban and SSR126768A, delivered via the same route lowered analgesia (Mazzuca et al., 2011). This is of interest as there is clinical evidence of stress-induced analgesia in spontaneously delivered newborn infants (Bergqvist et al., 2009). It was concluded, that the same hormone (oxytocin) that triggers delivery also acts as a natural pain killer in the fetus at birth (Mazzuca et al., 2011). Of note, the OTR antagonist atosiban employed in these experiments bind more readily to VR1A than to OTR (Akerlund et al., 1999) whereas SSR126768A is more OTR specific (Serradeil-Le Gal et al., 2004).

However, also very recently, elegant experiments with transgenic mice lacking the OTR or VR1A clearly demonstrated the indispensable prerequisite of VR1A for oxytocin-induced analgesia, at least at the peripheral level (Schorscher-Petcu et al., 2010). Systemically administered oxytocin was found to produce robust, dose-dependent analgesia in OTR KO mice but not in VR1A KO mice in a battery of thermal, mechanical, and chemical

nociception assays (Schorscher-Petcu et al., 2010). In addition, the analgesic effects of oxytocin could be fully prevented by a VR1A-selective antagonist, but not by an OTR-selective antagonist at the peripheral level (Schorscher-Petcu et al., 2010).

It is tempting to reinterpret the results of Mazzuca et al. (2011) in the light of the results from transgenic mice (Schorscher-Petcu et al., 2010). In both studies analgesia was studied at the peripheral level, the drugs were administered the same route, intraperitoneally. But there are many disparities between the studies of Mazzuca et al. (2011) and Schorscher-Petcu et al. (2010), including the species applied, rats vs. mice, the different ages, newborn pups vs. adults, the different pain assays, and the different OTR antagonists, atosiban (Akerlund et al., 1999), and SSR126768A (Serradeil-Le Gal et al., 2004) vs. desGly-NH₂-D(CH₂)₅[D-Tyr²,Thr⁴]OVT (Manning et al., 1995), respectively. In processing analgesia the spinal cord is an important switching point. There is convincing evidence from rat studies that the pain-relevant laminae of the dorsal horn express the OTR (Reiter et al., 1994; Tribollet et al., 1997; Veronneau-Longueville et al., 1999) and are a likely target of spinal oxytocin-ergic projections from the PVN of the hypothalamus (Swanson and Kuypers, 1980; Puder and Papka, 2001; Condes-Lara et al., 2007). Schorscher-Petcu et al. (2010) demonstrated a similar distribution of OTR and VR1A in mice and rats by an autoradiographic study on spinal cord sections, suggesting that at the spinal level no species differences exist. However it is not known, whether this receptor distribution is subject to developmental changes from birth to adulthood.

In order to verify the involvement of vasopressin-VR1A-signaling in mediating analgesia in newborn pups, new studies are warranted. But it has to be considered that the involvement of vasopressin and VR1A in analgesia is even more complex. Recently it was shown in mice and men that pain sensitivity and vasopressin analgesia are mediated by a gene-sex-environment interaction (Mogil et al., 2011). Vasopressin mediated analgesia was ameliorated in subjects with preceding stress-induced analgesia and in those harboring a nucleotide polymorphism in the gene coding for VR1A, which is male-specific (Mogil et al., 2011).

In conclusion, we propose in human newborns a much stronger involvement of vasopressin and VR1A in mediating analgesia than noted so far based on the following reasons: First, no exchange of vasopressin or oxytocin across placenta was demonstrated in humans *in vivo*. Second, human fetuses independently produce both hormones and toward the end of gestation there is marked increase in the vasopressin/oxytocin ratio in the pituitary (Schubert et al., 1981). Third, normal vaginal delivery evokes a dramatic surge in vasopressin and if at all only a minor increase in fetal oxytocin concentrations. Fourth, the VR1A receptor appears to be central in vasopressin- and oxytocin-induced analgesia, but featured with much greater affinity for vasopressin than oxytocin.

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